bjh short report

Comparative study of therapy-related and de novo adult b-cell acute lymphoblastic leukaemia

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Summary

We report a comparative analysis of patients with therapy-related acute lymphoblastic leukaemia (tr-ALL) vs *de novo* ALL. We identified 331 patients with B-ALL; 69 (21%) were classified as tr-ALL. The most common prior malignancies were breast (23·2%) and plasma cell disorders (20·3%). Patients with tr-ALL were older (median 63·2 vs. 46·2 years, $P < 0.001$), more often female (66·7% vs. 43·5%, $P < 0·001$), and more likely to have hypodiploid cytogenetics (18·8% vs. 5·0%, $P < 0·001$). In multivariable analysis, patients with tr-ALL were less likely to achieve complete remission [odds ratio (OR) = 0·16, $P < 0·001$] and more likely to be minimal residual disease-positive (OR = 4·86, $P = 0·01$) but had similar OS after diagnosis and allo-haematopoietic cell transplantation.

Keywords: ALL, leukemia, FISH, therapy-related.

Introduction

Therapy-related acute lymphoblastic leukaemia (tr-ALL) is a recently recognized, but poorly defined entity with an estimated incidence of 3–9% of ALL cases.[1–4] Furthermore, most series combined tr-ALL with the so-called ALL with prior malignancy, a different entity that refers to patients with antecedent neoplasia but without exposure to cytotoxic therapy. Therapy-related ALL is associated with inferior survival outcomes compared to *de novo* ALL, partly because it has

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been shown to harbour high-risk genetic features, mainly hypodiploidy/near triploidy, *KMT2A* rearrangements, monosomies 5, 7 and 17, complex karyotype as well as mutations usually seen in myeloid malignancies, such as *DNMT3A, RUNX1* and *ASXL1*.[3,5,6] The role of allogeneic haematopoietic cell transplantation (allo-HCT) is not well described; however, some reports suggested that it might abrogate the poor prognosis associated with tr-ALL despite being associated with increased non-relapse mortality.[5–7]

Herein, we report a comparative analysis of patients with *de novo* ALL and tr-ALL to characterize the different clinical and cytogenetic features as well as outcomes between these two entities.

Materials and methods

After approval from the Mayo Clinic Institutional Review Board, we identified patients who received at least one cycle of therapy or allo-HCT for b-cell (B)-ALL between 1 January 2008 and 31 December 2019 at the Mayo Clinic Cancer Center.

We defined tr-ALL as ALL developing after prior exposure to cytotoxic chemotherapy or radiation for another malignancy. Patients were classified into the following cytogenetic groups: (i) Philadelphia chromosome positive (Ph^+), t(9;22)(q34;q11.2)/*BCR-ABL1* fusion; (ii) *KMT2A* rearrangement; (iii) t(1;19)(q21;p13.3)/*TCF3-PBX1* fusion; (iv) hypodiploidy (30-39 chromosomes)/near triploidy (60-78 chromosomes); (v) hyperdiploidy (50-65 chromosomes); (vi) Philadelphia-like, as previously described[8]; (vii) t(12;21)(p13;q22)/*ETV6-RUNX1* fusion; (viii) normal karyotype and fluorescence *in situ* hybridization (FISH) panel; (ix) *CDKN2A/p16* deletion; (x) 14q32 translocations/IGH rearrangements; (xi) complex karyotype, (≥5 chromosomal abnormalities in the absence of other class defining genetic alterations); and (xii) Others. Measurable residual disease (MRD) was measured using a flow cytometry assay with a sensitivity of 0·01% at the end of induction.

Statistical analysis

Comparisons of characteristics between tr-ALL patients and *de novo* ALL patients were made using a Wilcoxon rank sum test and Fisher's exact test. Associations of tr-ALL with complete remission (CR) and MRD were examined using unadjusted and multivariable logistic regression models, where odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. For death after diagnosis and death after transplant, these were compared between tr-ALL patients and *de novo* ALL patients using unadjusted and multivariable Cox proportional hazards regression models; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Kaplan-Meier survival estimates, and 95% CIs were also calculated, where censoring occurred on the date of last follow-up. For relapse and non-relapse mortality (NRM), cumulative incidences and 95% CIs were estimated while accounting for competing risks. Multivariable logistic and Cox regression models were adjusted for baseline variables that differed between tr-ALL and *de novo* ALL with a P-value < 0·05 and that had <5% missing data, allowing no more than one variable in the model for each ten events per recommended guidelines.[9] In tr-ALL patients, the latency period was compared between cytogenetic groups using a Kruskal–Wallis rank sum test. P-values < 0·05 were considered statistically significant. Statistical analyses were performed using R Statistical Software (version 3·6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

We identified 331 patients with B-ALL, of whom 69 (21%) were classified as tr-ALL. A comparison of characteristics between tr-ALL and *de novo* ALL patients is shown in Table I. Prior malignancies and cytotoxic therapies are summarized in Table SI. The most common prior malignancies among tr-ALL patients were breast (23·2%), plasma cell disorder (20·3%), lymphoproliferative (17·4%), myeloid (14·5%) and genitourinary/gynaecologic (11·6%) malignancies. Chemotherapy was used in 59 (85·5%) patients, which included alkylating agents in 17 (24·6%) patients, topoisomerase II inhibitors in 4 (5·8%), and both in 19 (27·5%). Twenty-five (36·2%) patients were treated with radiation therapy and 15 (21·7%) patients had concurrent chemoradiation. Median latency period between exposure to prior cytotoxic therapy and development of tr-ALL was five years (range: 1–29 years) and was significantly longer for Philadelphia-positive compared to Philadelphia-negative B-ALL (median eight vs. four years, $P = 0.02$).

Compared with *de novo* ALL, patients with tr-ALL were older (median 63·2 vs. 46·2 years, $P < 0·001$), more often female [46 (66·7%) vs. 114 (43·5%), $P < 0·001$], less frequently of Hispanic ethnicity [2 (3·5%) vs. 34 (14·2%), $P = 0.02$] and had a lower median white blood cell (WBC) count on presentation (4·0 vs. 10·0 × 10^9/l, $P = 0·003$). Regarding cytogenetic subgroups, tr-ALL patients were more likely to have hypodiploidy/near triploidy [13 (18·8%) vs. 13 (5·0%), $P < 0·001$] and less likely to have Ph-like ALL [0 (0·0%) vs. 21 (8·0%), $P = 0·01$]. There was a similar incidence of Ph+ ALL in both groups [20 (29·0%) vs. 99 (37·8%), $P = 0.21$]. Patients with tr-ALL were less likely to receive paediatric-inspired regimens [2 (2·9%) vs. 49 (18·7%), $P < 0·001$] and less likely to proceed to allo-HCT [34 (49·3%) vs. 185 (70·6%), $P = 0·001$]. There were no differences between the two groups in ALL status at transplant (CR1 vs higher), donor type or graft type; however, patients with tr-ALL were less likely to have received a myeloablative conditioning regimen [15 (44·1%) vs 149 (81·0%), $P < 0·001$].

Table I. Comparison of characteristics between therapy-related ALL patients and *de novo* ALL.

Variable	*n*	Median (minimum, maximum) or No. (%) of patients		*P*-value
		Therapy-related ALL patients (*N* = 69)	*De novo* ALL patients (*N* = 262)	
Age at diagnosis (years)	331	**63.2 (18.2, 83.5)**	**46.2 (17.7, 88.8)**	**<0.001**
Sex (male)	331	**23 (33.3%)**	**148 (56.5%)**	**<0.001**
Race	320			0.55
White		59 (92.2%)	219 (85.5%)	
Black		2 (3.1%)	8 (3.1%)	
Asian		2 (3.1%)	8 (3.1%)	
American Indian/Alaskan Native		0 (0.0%)	8 (3.1%)	
Other		1 (1.6%)	13 (5.1%)	
Ethnicity (Hispanic or Latino)	297	2 (3.5%)	34 (14.2%)	**0.024**
WBC at diagnosis (x 10^9/L)	271	4.0 (0.5, 135.0)	10.0 (0.0, 700.0)	**0.003**
Hb at diagnosis (g/l)	251	98 (54, 148)	90 (0.0, 166)	0.12
Platelets at diagnosis (/μl)	255	64.0 (8.0, 313.0)	45.5 (0.0, 519.0)	0.11
Cytogenetic group	331			**<0.001**
t(9;22) BCR/ABL1		20 (29.0%)	99 (37.8%)	0.21
MLL (KMT2A) rearrangement		5 (7.2%)	11 (4.2%)	0.34
t(1;19) TCF3/PBX1		2 (2.9%)	5 (1.9%)	0.64
Hypodiploidy/near triploidy		13 (18.8%)	13 (5.0%)	**<0.001**
Hyperdiploidy (HeH)		3 (4.3%)	14 (5.3%)	1.00
Ph-like		0 (0.0%)	21 (8.0%)	0.01
Normal karyotype + FISH		6 (8.7%)	29 (11.1%)	0.67
Other		14 (20.3%)	39 (14.9%)	0.27
CDKN2A (p16) deletion		2 (2.9%)	10 (3.8%)	1.00
IGH rearrangements		0 (0.0%)	6 (2.3%)	0.35
Complex		4 (5.8%)	15 (5.7%)	1.00
Induction chemo	331			**<0.001**
HyperCVAD		38 (55.1%)	169 (64.5%)	
Paediatric regimens		2 (2.9%)	49 (18.7%)	
ECOG regimens		9 (13.0%)	23 (8.8%)	
Others		20 (29.0%)	21 (8.0%)	
CNS involvement	331	9 (13.0%)	23 (8.8%)	0.36
Allo-HCT	331	**34 (49.3%)**	**185 (70.6%)**	**0.002**
ALL status at allo-HCT	218			0.81
CR1		27 (79.4%)	150 (81.5%)	
≥ CR2		7 (20.6%)	34 (18.5%)	
Graft type	218			1.00
Bone marrow		2 (5.9%)	11 (6.0%)	
Peripheral blood		31 (91.2%)	163 (88.6%)	
Umbilical cord		1 (2.9%)	10 (5.4%)	
Donor type	218			0.10
Matched related		15 (44.1%)	60 (32.6%)	
Haploidentical		4 (11.8%)	11 (6.0%)	
Matched unrelated		15 (44.1%)	113 (61.4%)	
Conditioning regimen	218			**<0.001**
Myeloablative		15 (44.1%)	149 (81.0%)	
Reduced intensity		19 (55.9%)	35 (19.0%)	

P-values result from a Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables). For cytogenetic group, and overall test of difference was performed followed by separate tests for each individual cytogenetic group. Statistically significant results are shown in bold. ALL, acute lymphoblastic leukemia; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence *in situ* hybridization; HCT, haematopoietic cell transplantation; HyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; WBC, white blood cell count.

Outcomes

At the end of induction, 307 (92·7%) patients achieved a complete remission (CR) and 43 (42·6%, $n = 101$) patients were MRD-positive; a summary of outcomes can be found in Table II. In multivariable analysis adjusting for potential confounding variables, patients with tr-ALL had a significantly lower likelihood of achieving a CR (OR = 0·16, $P < 0·001$) and a higher likelihood of being MRD-positive when in remission (OR = 4·86, $P = 0·01$).

Median length of follow-up was 2·5 years (range: 7 days–18·0 years). Patients with tr-ALL had an inferior OS after diagnosis in unadjusted analysis, with a three-year OS of 40·2% compared to 63·8% for *de novo* ALL (HR =2·02, $P < 0·001$, Fig S1A); however, in multivariate analysis this difference weakened substantially and no longer approached statistical significance (HR = 1·17, $P = 0.47$). No statistically significant difference in OS after transplant between the two groups was noted in the subgroup that underwent allo-HCT in multivariable analysis (HR = 1·00, $P > 0·99$). Similarly, no significant differences between tr-ALL and *de novo* ALL groups were noted regarding relapse (HR = 1·24, $P = 0·46$) or NRM (HR = 1·04, $P = 0·91$) in multivariable analysis.

Discussion

We report a series of patients with therapy-related ALL using a strict definition of prior exposure to cytotoxic chemotherapy and/or radiation. In our cohort, patients with tr-ALL were older, less likely to achieve CR, more likely to be MRD-positive at the end of induction and had higher risk cytogenetics. Although patients with tr-ALL had an inferior OS in unadjusted analysis, this difference was greatly attenuated in multivariable analysis. We also noted that outcomes after allo-HCT (OS, NRM and relapse) were similar for both groups in multivariable analysis; this is likely the result of selection bias, where patients who are younger and more fit in the tr-ALL group received intensive up-front therapy and were able to proceed to allo-HCT.

Patients with tr-ALL were also more likely to be female than *de novo* ALL patients, likely a reflection of breast cancer as the most common primary malignancy. Another interesting demographic difference between the two groups was the lower likelihood of being of Hispanic ethnicity in the tr-ALL group, which coincides with the difference in Ph-like ALL incidence in both groups.

In our cohort, we noted a higher incidence of tr-ALL (21%) than what was previously reported in literature, which we attributed to referral patterns in the Mayo Clinic Cancer Center and enrichment of our cohort with patients with plasma cell disorders who are exposed to alkylating agents and immunomodulators along their treatment course. Three large phase 3 clinical trials have demonstrated a significant increased risk of secondary primary malignancies associated with lenalidomide maintenance following high-dose melphalan.[10–12] The secondary primary malignancy risk ranged from 8% to 17% with 4–17% of those malignancies being haematologic malignancies without specifying the percentage of ALL cases. A recent study of 13 tr-ALL cases by Aldoss *et al*. analyzed paired samples of multiple myeloma and ALL using whole-exome sequencing and reported that tr-ALL arising in this setting is clonally unrelated to the multiple myeloma, supporting the notion that it represents a therapy-related leukaemia.[13] Further research on tr-ALL in patients with antecedent multiple myeloma is warranted.

Patients with tr-ALL were more likely to have hypodiploid karyotype than patients with *de novo* ALL with deletions involving chromosome 17 as well as other monosomal chromosomes (e.g. chromosomes 5 and 7), this is consistent with previous reports and is likely a reflection of mitotic instability as a result of prior exposure to cytotoxic therapy.[6,14] Another interesting observation is the occurrence of Ph+ ALL in the tr-ALL group with a similar incidence in the *de novo* ALL group. Ph+ ALL was also the most common genetic alteration in several series of tr-ALL,[5,15] supporting the notion that *BCR/ABL1* fusion can occur as a therapy-related abnormality after exposure to cytotoxic therapy.[16]

Acknowledging the limitations of our study (e.g. retrospective design, relatively small sample size and corresponding possibility of type II error), our results support the recognition of tr-ALL as an important and unique clinical entity that deserves further investigation, as it is associated with distinctive and adverse cytogenetic and clinical features.

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Conflicts of interest

The authors have no relevant conflicts of interest.

Author contributions

ZHA, RDP, MGH, NW and KCM performed data collection, contributed to research design, and analyzed the data. HA, LS, HSM, WJH, MAK, JFP, LBB, NH, RK, MRL, PTG and JMF contributed to research design, analysis and interpretation of data. All authors participated in drafting the paper, revising it critically and approved the final version.

Table II. Comparison of outcomes between therapy related and *de novo* ALL.

Outcome/patient group	Number (%) of patients with the outcome	Cumulative incidence (%) at 3 years (95% CI)	Association measure	Unadjusted analysis		Multivariable analysis	
				Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
MRD (positive)			Odds ratio				
De novo ALL	28/80 (35.0)	N/A		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	15/21 (71.4)	N/A		**4.64 (1.69, 14.27)**	**0.004**	**4.86 (1.47, 18.41)**	**0.013**
Complete remission			Odds ratio				
De novo ALL	252/262 (96.2)	N/A		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	55/69 (79.7)	N/A		**0.16 (0.06, 0.37)**	**<0.001**	**0.16 (0.06, 0.43)**	**<0.001**
Survival after ALL diagnosis			Hazard ratio				
De novo ALL	N/A	63.8 (58.1 – 70.2)		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	N/A	40.2 (28.5 – 56.6)		**2.02 (1.39, 2.94)**	**<0.001**	1.17 (0.77, 1.77)	0.47
Survival after allo-HCT			Hazard ratio				
De novo ALL	N/A	61.9 (54.9 – 69.8)		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	N/A	48.6 (31.2 – 75.7)		1.42 (0.82, 2.48)	0.21	1.00 (0.54, 1.85)	1.00
Relapse			Hazard ratio				
De novo ALL	N/A	27.4 (22.3 - 33.6)		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	N/A	31.1 (20.6 - 46.9)		1.34 (0.79, 2.28)	0.27	1.24 (0.70, 2.22)	0.46
Non-relapse mortality			Hazard ratio				
De novo ALL	N/A	17.9 (13.0 - 24.6)		1.00 (reference)	N/A	1.00 (reference)	N/A
Therapy-related ALL	N/A	35.5 (19.7 - 64.0)		1.80 (0.90, 3.63)	0.099	1.04 (0.48, 2.29)	0.91

Odds ratios, 95% CIs, and *P*-values result from logistic regression models. Hazard ratios, 95% CIs, and *P* -values result from Cox proportional hazards regression models. Multivariable models were adjusted for baseline variables that differed between *de novo* ALL and therapy-related ALL groups with a *P* -value < 0.05 and that had <5% missing data (excluding the Ph-like cytogenetic group, which could not be adjusted for due to the presence of a zero cell count), allowing no more than one variable in the model for each 10 'events' per recommended guidelines, where an event is the minimum sample size of the two outcome categories in logistic regression, and the number of patients who experienced the outcome in Cox regression. These variables were age at diagnosis, sex, Ho-Tri (outcomes of MRD and non-relapse mortality), age at diagnosis (outcome of complete remission), and age at diagnosis, sex, Ho-Tri, and induction chemo (outcomes of survival after ALL diagnosis, survival after allo-HCT, and relapse). Statistically significant results are shown in bold. ALL, acute lymphoblastic leukemia; CI, confidence interval; HCT, haematopoietic cell transplantation; MRD, measurable residual disease.

Data availability statement

Please contact the corresponding author at foran. james@mayo.edu.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Prior malignancy and cytotoxic therapy for patients with therapy-related acute lymphoblastic leukaemia (tr-ALL).

Fig S1. Unadjusted comparison of overall survival between de novo and therapy-related acute lymphoblastic leukaemia (tr-ALL) in the overall cohort (A) and the allogeneic transplant cohort (B).

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